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REMARKS

It is respectfully requested that this application be reconsidered in view of the following remarks and that all of the claims remaining in this application be allowed.

Claims 16 and 20-32 are pending in this application. Claims 1-15 and 17-19 were previously canceled.

Rejections under 35 U.S.C. 103 (a)

Claims 16 and 20-32 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over McCrory, U.S. Patent 5,951,599, in view of Chuter et al., (J Vasc Surg 2000; 31:122-33), May (J Vasc Surg 2000; 32:124-129) and Evans et al., U.S. Patent 5,695,480.

This rejection is traversed because neither the cited Chuter nor the cited May references constitute prior art against the claimed invention. Specifically, this application is a divisional of U.S. Patent Application Serial No. 09/528,656, now U.S. Patent No. 6,475,466, which, in turn, is a continuation-in-part of U.S. Patent Application Serial No. 09/273,120, now U.S. Patent No. 6,203,779 B1 (the '779 patent). The '779 patent has an effective filing date of March 19, 1999 which is prior to both the cited Chuter and May publications dates both of which were published in 2000.

The USPTO alleges that Applicants are not entitled to the March 19, 1999 priority date of the ultimate parent to this application because "March 2000 is the earliest time the Applicants appear to have envisioned the use of stent-grafts in their kits".[1] However, this is simply incorrect.

Applicants note that the '779 patent recites at Col. 4, lines 19-33, a kit of parts which comprises the following components:

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[1] See, footnotes 1 and 2 bridging pages 2 and 3 of the Office Action.

"(a) a fluid composition which forms a coherent mass in the presence of blood which mass adheres to the vascular surface and/or the surface of the endovascular prosthesis;

(b) a catheter suitable for delivering the fluid composition to an endoleak site formed from endovascular repair of an aneurysm; and

(c) a catheter suitable for delivering an endovascular prosthesis to the aneurysm.

In a preferred embodiment, this kit further comprises an endovascular prosthesis."

A copy of the '779 patent is enclosed for the convenience of the USPTO.

Col. 7, lines 13-15, of the '779 patent recites that the fluid composition comprises a biocompatible solvent, a biocompatible polymer and optionally a contrast agent. Col. 9, lines 29-32, of the '779 patent further recite that the described methods are for

"...the catheter assisted sealing of endoleaks formed by endovascular repair of an abdominal aortic aneurysm by an endovascular prosthesis."

Accordingly, all of the elements of parts (a), (b) and (c) are found in the ultimate parent application.

As to element (d) of now presented Claim 16, this element recites "an endovascular prosthesis comprising a stent graft capable of inhibiting but not completing arresting blood flow into the abdominal aortic aneurysm due to the presence of one or more endoleaks." As noted above, the ultimate parent application recites the kit preferably further comprises an endovascular prosthesis. Moreover, the specification at Col. 9, lines 33-37, of the '779 patent recite:

"...endovascular repair of such aneurysms involves the introduction of an endovascular prosthesis into the abdominal aortic aneurysm which is an art recognized procedure described, for example, by Parodi[17]".

Parodi, in turn, recites in its very title "Endovascular AAA ***Stent Grafts***: Technology, Training and Proper Patient Selection" (emphasis added). This reference was incorporated by

reference in its entirety into the ultimate parent application. A copy of the Parodi reference is enclosed for the convenience of the USPTO.

Additionally, Example 2 of the '779 patent recites the use of a Wallgraft. Such Wallgrafts are recognized in the art as stent grafts. See, for example, the Materials and Methods section of Cejna, et al., J. Vasc. Inter. Radiol. 13:823-830 (2002). A copy of this reference is enclosed for the convenience of the USPTO..

Accordingly, the ultimate parent application clearly contemplated the use of stent grafts as an endovascular prosthesis.

It is, therefore, incorrect for the Office to assert that the original filed application failed to contemplate stent grafts in their kits.

Since both the May and Chuter references do not constitute prior art against the claimed invention, withdrawal of this rejection is requested.

Claims 16 and 20-32 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Evans, U.S. Patent 5,702,361 in view of Chuter, *supra*.

As before, the cited Chuter reference does not constitute prior art against the claimed invention and, accordingly, this rejection is in error.

Withdrawal of this rejection is requested.

CONCLUSION

In view of the above, Applicants submit that this application is now in condition for allowance. A notice to that effect is earnestly solicited.

If it is determined that a telephone conversation would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872, docket number 355492-2202. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872, docket number 355492-2202. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872, docket number 355492-2202.

Respectfully submitted,

Date 7-21-04

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Technology, Training and Proper Patient Selection

Juan C. Parodi, M.D.
Combined Session: Vascular Surgery and Interventional Radiology

Medical Industries finally got involved in the stent-graft technology, probably they started to learn the impact of these new methods on the vascular diseases' therapy arena. Use of home made systems are currently generally restricted to those cases with a very unusual anatomy that are not suitable for the use of any device produced by the industry.

Thin resistant vascular fabric grafts have been developed and most of the companies incorporated those very thin graft in their products. These thin grafts allowed the practitioners to use low profile devices. Polyester woven grafts were the favorites; PTFE has been used in some devices but to obtain the thickness utilized in the Polyester fabric graft, the resistance to dilatation had to be compromised.

Different metal components of devices blended with fabric grafts resulted in modular systems adaptable to most of the anatomical variations of aneurysms.

Tubular devices are seldom used for AAA since mid and long term results using them have been unacceptable. The aorto-bi-iliac configuration is by far the favorite one. Aorto-uni-iliac device finds application in some complicated cases with unfavorable anatomy to apply the bifurcated configuration.

Nitinol (Nickel-Titanium Alloy) is the stent component more popular among devices. The super-elastic and the nitinol with thermal memory are the two types utilized.

Some devices place the graft inside the metallic frame (AneuRx, Talent), some others on the inside (Vanguard). In theory to have the graft inside has advantage over the other because the inner surface is smoother and less prone to form thrombus.

Crossing the renal arteries ostium appears as a valuable alternative to be used in clinical cases in which the proximal neck is short. It is well known that the wall strength of the aorta at the level of the branches is stronger due to the presence of intercrossing adventitial fibers that come from the branches, in this case the renal arteries. Few cases of renal artery embolization and occlusion were reported but appears that for most of the cases the technique is safe. It is expected however that special bare stent configurations could be developed by the Medical Industries for those cases in which the renal arteries will be covered by the stent.

Balloon expandable stents were the first utilized in this field, balloon rupture and balloon displacement with flow and pressure made those systems more cumbersome than the self expandable, spring loaded stents. Material fatigue has been an issue brought by the follow up studies, hook fracture happened as well as suture breakage. Those problems have been addressed and for the most part solved by the industry.

Development of co-extruded systems are in process. They will have several advantages in terms of avoiding the "wind sock effect" in the moment of deployment. This new systems in which the stent is introduced in a different sheath than the graft provides the solution to flow interruption during deployment. Blood flow passes through the interstices foe the stent while the system is deployed. This system is expected to be very useful to treat thoracic aortic aneurysms and dissections.

Endosutures have also been developed. They could be used in cases of short and dilated necks. Testing will disclose its long term durability. Method of "endosuturing" is described in a different presentation of this meeting.

Training

In vitro flow models allow appropriate training for interventionists, they are more practical than the animal models. Training using human cadavers provide a closer to the reality scenario. Assisting experienced surgeons in several cases and having expert persons assisting the beginners on their first cases completes an acceptable method of training.

Endoluminal treatment of AAA is not a simple procedure, it is not reasonable to start doing complex endovascular procedures before grad-

ually being involed in progressively more technically demanding procedures. It is advisable for the surgeons to gain experience with guidewires, catheters and introducer sheaths doing diagnostic procedures first, the second step is to do simple iliac or superficial femoral arteries and angioplasties, to deploy inferior Vena Cava filters and to use some balloon expandable and self expandable stents before embarking in endoluminal treatment of AAA. Surgical Societies are in the process of regulating Credentials to insure appropriate application of this new technology.

Patient Selection

Endoluminal treatment of AAA is still an experimental procedure, thus, the two main application of the method are: Patients included in a clinical trial and patients with large aneurysms considered to be in the group of prohibitive risk to have the standard open procedure.

Proper patient selection results in excellent results in centers with extensive experience on using endovascular treatment of AAA. After gaining experience some centers have embarked in the treatment of more complex patients and anatomical situations.

Essentially a good candidate for this technique is a patient with an AAA otherwise healthy, not very obese with straight arteries, proximal neck of 2 cm or more, common iliac arteries of more than 7mm and less than 11mm in diameter. No stenosis or occlusion of the iliac axis. Some systems tolerate small angulations (less than 60 degrees) of the proximal neck. Tortuosity of the iliac arteries can be handled by the "pull down technique" described by us, the use of stiff wires and the application of a through and through guidewire inserted from the brachial artery down to the femoral artery, applying gentle tension to the wire usually straightens the iliac axis. Heavily calcified tortuous arteries are still a challenge for accessing the aorta. Lower profile and more flexible systems have helped to overcome some of those difficult situations, if the indication is sound, facing a serious problem of access can be solved by creating a temporary access implanting a graft onto the common iliac artery bringing the other end to the inguinal area.

In centers with a large experience, patients with unfavorable anatomy can be treated with reasonable success rate. Those indications, however, should be made with great caution, aneurysms should be large enough or even symptomatic to insure that the risk/benefit ratio justifies the endoluminal treatment.

Some patients face more risk of embolization during endoluminal treatment of AAAs, those are patients who had spontaneous embolization in the past, irregular surface of mural thrombus on the CT Scan or double lumen of the aorta. This group of patients should be treated using a different technique. Acess is gained from the brachial artery using a 6Fr. Introducer. A long 4 Fr Swan-Ganz is inserted into the brachial artery and advanced into the thoracic aorta, the balloon is inflated and the balloon is let to navigate with flow, the abdominal aorta is reached and without disturbing the thrombus the balloon is retrieved from the femoral arteriotomy and an extra-still guidewire inserted creating a through and through wire connection from the brachial artery to the femoral artery, in this way penetration of the wire into the thrombus is prevented diminishing the risk of embolization caused by disruption of the thrombus.

NOTES

Biocompatibility and Performance of the Wallstent and the Wallgraft, Jostent, and Hemobahn Stent-Grafts in a Sheep Model

Manfred Cejna, MD, Renu Virmani, MD,[1] Russel Jones, Helga Bergmeister, DVM, MD, Christian Loewe, MD, Maria Schoder, MD, Mario Grgurin, MD, and Johannes Lammer, MD

PURPOSE: Three recently developed stent-grafts and the Wallstent were compared directly in an ovine animal model with regard to performance and biocompatibility.

MATERIALS AND METHODS: Three stent-grafts, the Hemobahn (polytetrafluoroethylene [ePTFE]/nitinol), Wallgraft (polyester/Ni-Co-Ti-steel alloy), and Jostent peripheral stent-graft (balloon-expandable ePTFE/stainless steel), and the Wallstent (Ni-Co-Ti-steel alloy), were implanted in sheep iliac arteries (one type of each stent or stent-graft per animal, $n = 8$). Pre- and postimplantation luminal diameters were measured for each prosthesis and implantation site. Angiography, intravascular ultrasonography (IVUS), and histomorphometric, histologic, and scanning electron microscopic analyses were performed at 3 months.

RESULTS: Early lumen gain, late lumen loss, and patent vessel diameter at angiography were not significantly different. Two stent-grafts had significantly more neointima formation (Hemobahn, 9.88 $mm^2 \pm 0.94$; Wallgraft, 14.98 $mm^2 \pm 0.90$) than the other stent-graft (Jostent, 6.52 $mm^2 \pm 0.46$) and the Wallstent (5.24 $mm^2 \pm 0.62$; $P < .01$). Patent lumen area was not significantly different (Hemobahn, 42.57 $mm^2 \pm 1.41$; Jostent, 39.76 $mm^2 \pm 2.04$; Wallgraft, 40.22 $mm^2 \pm 1.04$; Wallstent, 41.64 $mm^2 \pm 1.59$; $P = .57$). The Hemobahn had significantly more inflammatory reaction (inflammation score of 0.83 ± 0.03) than the Jostent (0.58 ± 0.03), Wallgraft (0.55 ± 0.04), or Wallstent (0.16 ± 0.01). Angiography and IVUS demonstrated absence of anastomotic neointima formation. Endothelialization was incomplete and immature for all prostheses.

CONCLUSIONS: The stent-grafts caused a greater degree of neointima formation and inflammatory vessel wall reaction than the bare stent. However, these changes did not interfere with patent lumen areas and occurred in the absence of excessive anastomotic neointima formation.

Index terms: Endovascular stent-grafts • Intimal hyperplasia • Restenosis • Stents and prostheses

J Vasc Interv Radiol 2002; 13:823–830

Abbreviations: IVUS = intravascular ultrasound, SMC = smooth muscle cell

RESTENOSIS after stent implantation remains a significant limitation after coronary and peripheral stent implantation (1,2). Clinical and histologic studies have characterized the mechanism of in-stent restenosis as intimal hyperplasia initiated by the proliferation of smooth muscle cells (SMCs) in response to acute injury (3,4).

Fabric-covered metal stents (stent-grafts) were first used clinically for endovascular treatment of aneurysms (5,6) and have been used additionally for effective treatment of arterial occlusive disease (7–9). The purpose of the fabric coating on stent-grafts is to inhibit the migration of SMCs through the fabric and prevent the formation of neointimal hyperplasia (7–9). Additionally, stent-grafts are increasingly used to treat complications of percutaneous interventions such as perforations and pseudoaneurysm formations (10–12).

Still, little is known about comparative biocompatibility (induction of vessel wall inflammatory reaction) and performance (early lumen gain, late lumen loss, neointima formation) of stent-grafts. For this purpose, we undertook a direct comparison by implanting stent-grafts and a bare stent in paired normal ovine iliac arteries.

MATERIALS AND METHODS

Animal Preparation and Endoprostheses

All animal care and handling was performed in accordance with the

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[1] This author has disclosed the existence of a potential conflict of interest. No other author has identified a conflict of interest.

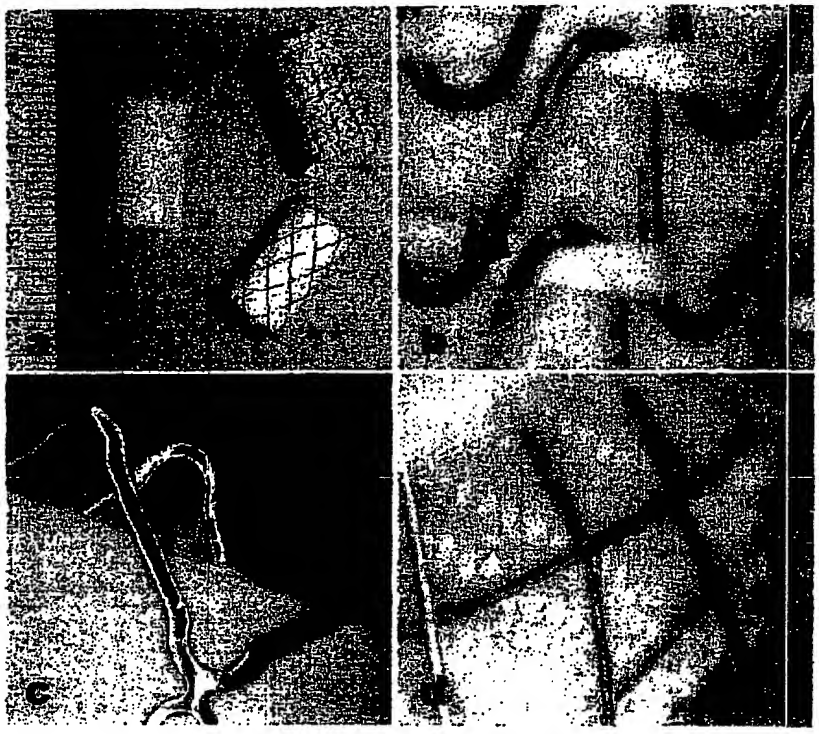

Figure 1. (a) The stent-grafts used in the study (*, Hemobahn; **, Jostent; ***, Wallgraft). Close-up (magnification ×10) of the Hemobahn stent-graft (b), which consists of an ePTFE tube inside nitinol, sinusoidal-shaped, helically wrapped stents. The nitinol wire structure is secured to the ePTFE tube by fluorinated ethylene propylene and ePTFE tape (arrowheads). (c) The Jostent peripheral stent-graft is a balloon-expandable stainless-steel (316L) stent that remains rigid longitudinally. The stent is composed by a sandwich construction of two bare peripheral Jostent slotted stents with a thin layer of ePTFE wrapped between them (total wall thickness of 0.3 mm). (d) The Wallgraft endoprosthesis is a flexible self-expanding endovascular prosthesis with polyethylene terephthalate (polyester) fabric on the outside and cobalt-based alloy monofilament wires on the inside. Three tracer wires (platinum–nickel) are incorporated for better visibility.

guidelines specified by the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Vienna. Thirty-two prostheses (Fig 1) —Hemobahn (self-expandable nitinol structure with internal expanded polytetrafluoroethylene [ePTFE]; n = 8, 7–9-mm diameter, 50-mm length; W.L. Gore and Associates, Flagstaff, AZ), Jostent peripheral stent-graft (balloon-expandable ePTFE sandwich construction with 316L steel stent; n = 8, 4–9-mm diameter, 38-mm length; Jomed, Beringen, Switzerland), Wallgraft (self-expanding cobalt-based alloy monofilament wire stent with external polyethylene terephthalate fabric; n = 8, 8–10-mm diameter, 40-mm length; Boston Scientific/Medi-tech, Natick, MA) and eight Wallstents (self-expandable nickel-cobalt-titanium-steel wire stent; 8–10-mm diameter, 30-mm length; Boston Scientific/Medi-tech)—were implanted in the iliac arteries of eight female sheep and followed up for 3 months. The methods for tissue and stent processing have been described in detail in a previous publication (13).

Eight female sheep (shoulder height, approximately 65–70 cm; weight, 41–59 kg; mean weight, 50 kg) were used. The animals were fed a standard laboratory ovine diet with water provided as desired. Routine preoperative blood work with measurements of creatinine, blood urea nitrogen, bilirubin, fibrinogen, and hematocrit, total white blood cell count, and platelet count were performed.

Anesthesia was induced with thiopental (10 mg/kg body weight intravenously). After orotracheal intubation, anesthesia was maintained by volume-controlled ventilation with 1.5% volume isoflurane/nitric oxide/oxygen. The sheep were placed in dorsal recumbent position with the hind limbs in normal extended position with moderate abduction. The animals received an appropriate electrolyte fluid supplement during the surgical procedure. Before surgical cutdown, animals received 0.05 mg fentanyl intravenously. Animals were given 10 million IU benzylpenicillin (Penicillin G-Natrium; Biochemie Vienna, Vienna, Austria) and 2 g oxacillin (Stapenor; Bayer Austria, Vienna, Austria) as perioperative antibiotic prophylaxis and medication was continued over the course of the next 2 days.

A baseline activated clotting time test was performed before systemic heparinization (to achieve and maintain a minimum value of two times the initial baseline activated clotting time). Surgical cutdown of the common femoral artery was performed bilaterally, followed by placement of standard 10-F introducer sheaths. Calibrated angiography of the iliac vessels (5-F pigtail marker catheter; Cook, Bloomington, IN) was performed on a mobile Siemens C-arm angiography unit with digital subtraction angiography capabilities (Siremat 2000; Siemens, Erlangen, Germany). Intravascular ultrasonography (IVUS) was used for measurement of iliac artery diameter.

The Hemobahn endoprostheses used in the experiment were 7 mm (n = 2), 8 mm (n = 3), and 9 mm in diameter (n = 3). The Jomed stent-grafts were dilated to 8 mm (n = 6) or 9 mm (n = 2). The Wallgrafts were dilated to 8 mm (n = 8), the Wallstents to 8 mm (n = 7) and 9 mm (n = 1). IVUS confirmed optimum seating of the stent-graft after angioplasty (OPTA balloon, 15 sec at 6 atm; Cordis, Miami, FL). Each type of prosthesis was placed once per animal. Two prostheses were inserted on each side, one cranial and one caudal to the gluteal artery. The implantation sides varied, so each type of prosthesis was inserted twice in each possible location (together, n = 8 for each stent).

Animals were allowed to recover and then returned to care facilities, where they received a normal diet. Besides 40 mg of enoxaparin (Lovenox; Gerot Pharmaceuticals, Vienna, Austria) on the day after surgery, no oral anticoagulation or antiplatelet therapy was used in the follow-up period to facilitate neointima formation. Buprenorphine (Buprenex; Reckit and Colman, Hull, UK) was given twice daily (0.005 mg/kg body weight) for analgesia for 3 days. All animals exercised daily for the first week postoperatively. To rule out inflammatory response, blood samples (white blood cell count, fibrinogen and hematocrit levels, thrombocyte count) were measured weekly until 4 weeks after implantation. Body temperature was measured every day until 1 week after implantation and then weekly until 8 weeks after implantation and postoperative and preoperative values were compared.

The animals were returned to the operating room for angiography, IVUS, and implant retrieval 3 months after implantation and killed by intravenous administration of barbiturate and 1 mol/L (7.45 g per 100 mL) potassium solution. The iliac arteries, including the distal abdominal aorta and the proximal femoral arteries, were exposed, the major side branches were ligated, and pressure fixation with 7.5% paraformaldehyde was performed for 5 minutes. The iliac arteries were then removed en bloc and fixed in buffered formalin (7.5%) for at least 2 weeks.

IVUS and Angiographic Measurements

IVUS measurements were performed with a CVIS system (Critical Vision, Atlanta, GA) with manual pullback. The system was supplied with a 30-MHz, 5-F, mechanical US probe and examinations were recorded on an S-VHS VCR. Calibrated angiograms (5-F marker catheter; Cook) were scanned on a dedicated Lumisys 20 digital x-ray scanner (Lumisys, Sunnyvale, CA) and stored as TIFF files and analyzed with Osiris 4.0 software (University Hospital Geneva, Switzerland). The system was calibrated to the marker catheter. The baseline, postimplantation, and 3-month minimal lumen diameters within the stent (six measurements averaged per stent) were measured on digitized digital subtraction angiographic images.

Histopathologic Evaluation

Sample preparation was performed as described previously (13,14). The specimens in six animals (Nos. 1–6) were infiltrated with a polymer resin (Technovit 7200; Exakt Technologies, Oklahoma City, OK) after dehydration in ethanol. Blocks and slides were prepared. Three segments of each stent—transverse segments from the proximal, middle, and distal portions of the stent-graft—were obtained with use of the Exakt Cutting Grinding System (Exakt Technologies). The sections were surface-ground to 30–40 μm and stained with hematoxylin and eosin. Histomorphometric measurements were performed with use of digital image analysis (IP Lab Spectrum; Signal Analytics, Vienna, VA). Neointimal area was defined as the distance between the lumen surface and the inner layer of the cover. Neointimal thickness was calculated by averaging nine to 12 measurements. Additionally, we measured neointimal area luminal to the cover membrane (lumNA) or luminal to the internal elastic lamina (for the Wallstent) and calculated the ratio of luminal neointimal area to total neointimal area. The extent of vessel wall reaction was graded from 0 (absence of inflammation) to 3 (presence of dense accumulations of granulocytes, lymphocytes, or giant cells around the stent strut or stent-graft cover), calculated by averaging the sum of inflammation scores of eight sectors (eight 45° intervals).

Scanning Electron Microscopy

Scanning electron microscopy was performed in two of the eight retrieved specimens (Nos. 7 and 8) after they were rinsed in 0.1-mMol cacodylate buffer and fixed with 1% osmium tetroxide. Then the specimens were dehydrated in ethanol, spatter-coated in gold, and examined with a Zeiss scanning electron microscope (model DSM 960A; Zeiss, Oberkochen, Germany). The percentage of endothelium throughout the device was estimated visually by detailed scanning electron microscopic analysis. We evaluated the percentage of endothelial covering at six randomly selected sites from each stent at the proximal, middle, and distal stent portions ($n = 2$ each) at 500× magnification. Endothelialization is given as a percentage of total area and endothelial maturity was graded as either immature (polygonal-shaped) or mature (spindle-cell–shaped).

Statistical Analysis

The mean data for each stent were compared by one-way analysis of variance with Bonferroni correction for multiple comparisons. Data are indicated as means ± SEM. SPSS statistical software (SPSS, Chicago, IL) was used for all calculations. If a P value lower than .05 was calculated, all groups were also compared with Bonferroni correction.

RESULTS

Implantation Procedure and Follow-up

Implantation was technically successful in all stents and stent-grafts. All animals were symptom-free after implantation. In the follow-up period, there was no significant increase in white blood cell count, body temperature, or fibrinogen levels compared to preoperative values. IVUS demonstrated optimum seating in the proximal and distal anastomotic region against the vessel wall and complete expansion for all the stent-grafts after implantation and balloon dilation. Differences between patent mean lumen diameters before and after implantation and at 3 month follow-up were not significant between the groups ($P = .98$, $P = .30$, and $P = .96$, respectively). The patent vessel lumen diameters at follow-up angiography ranged from 6.61 mm ± 0.27 (Wallgraft) to 7.29 mm ± 0.21 (Jostent). There were no significant differences in early gain and late loss (with ranges from −1% ± 3% [Hemobahn] to −10% ± 2% [Wallgraft] in late lumen loss) between the prostheses. IVUS and angiography confirmed absence of luminal narrowing (≥5% diameter reduction) caused by neointima formation at the anastomotic regions (Table 1).

Histomorphometric Analysis

All stent sites were examined morphometrically at 3-month follow-up.

Table 1
Quantitative Angiography Analysis of Preimplantation, Postimplantation, and Preexplantation Vessel Lumen Diameters (in mm ± SEM)

Measurement		n	Mean	SEM	95% CI for Mean		ANOVA *P* Value
					Lower Bound	Upper Bound	
Preimplantation diameter	Hemobahn	8	7.18	0.49	6.77	7.59	
	Jostent	8	7.14	0.27	6.50	7.79	
	Wallgraft	8	7.23	0.24	6.67	7.79	
	Wallstent	8	7.30	0.32	6.54	8.05	.98
Postimplantation diameter	Hemobahn	8	7.26	1.06	6.37	8.14	
	Jostent	8	7.29	0.21	6.79	7.78	
	Wallgraft	8	6.61	0.27	5.97	7.25	
	Wallstent	8	7.00	0.21	6.50	7.50	.30
Preexplantation diameter	Hemobahn	8	7.34	0.67	6.77	7.90	
	Jostent	8	7.50	0.24	6.93	8.08	
	Wallgraft	8	7.36	0.24	6.79	7.93	
	Wallstent	8	7.46	0.26	6.84	8.07	.96
Early gain	Hemobahn	8	1.02	0.09	0.95	1.10	
	Jostent	8	1.05	0.01	1.02	1.08	
	Wallgraft	8	1.02	0.02	0.97	1.07	
	Wallstent	8	1.03	0.02	0.97	1.08	.76
Late loss	Hemobahn	8	0.99	0.10	0.91	1.07	
	Jostent	8	0.97	0.01	0.95	1.00	
	Wallgraft	8	0.90	0.02	0.86	0.94	
	Wallstent	8	0.94	0.03	0.88	1.00	.06

Note.—Early lumen gain and late lumen loss were calculated and averaged. ANOVA *P* values are indicated.

Cross-sections for all stent-grafts and the Wallstent are shown in Figure 2 and results are given in Table 2. There were no significant differences in patent lumen area between the prostheses (42.57 mm^2 ± 1.41 [Hemobahn], 39.76 mm^2 ± 2.04 [Jostent], 40.22 mm^2 ± 1.04 [Wallgraft], and 41.64 mm^2 ± 1.59 [Wallstent], $P = .57$). Wallgraft implantation resulted in modest neointimal growth that impacted vessel patency (14.98 mm^2 ± 0.90). The Hemobahn demonstrated less neointimal formation (9.88 mm^2 ± 0.94), but significantly greater than that of the Jostent (6.52 mm^2 ± 0.46) and Wallstent (5.24 mm^2 ± 0.62; $P = .02$ and $P < .01$, respectively). Mean intimal thickness was significantly different between the Wallgraft (0.56 mm ± 0.03) and the other prostheses (0.35 mm ± 0.03 [Hemobahn], 0.25 mm ± 0.01 [Jostent], and 0.23 mm ± 0.01 [Wallstent]; $P < .01$). Also significant were the differences between the Hemobahn and the Jostent and Wallstent ($P = .05$ and $P < .01$, respectively). A (minimal) intraluminal thrombus was observed on only one section (for the Hemobahn endoprosthesis, with a size <1 mm^2).

The ratio between luminal neointima and total neointima (as a percentage) was significantly higher for the Wallgraft (93% of total neointima, $P < .001$) compared to the other prostheses (Hemobahn, 21%; Jostent, 17%; Wallstent, 16%). The differences between the Hemobahn, Jostent, and Wallstent were not significant. Medial area was significantly lower for the balloon-expandable rigid Jostent (3.80 mm^2 ± 0.25; $P < .001$) than for the self-expandable prostheses (Hemobahn, 5.26 mm^2 ± 0.53; Wallgraft, 6.08 mm^2 ± 0.11; Wallstent, 5.26 mm^2 ± 0.24). There were no significant differences (lumen area or neointimal area) when proximal, central, and distal sections were compared for each prostheses.

Histopathology

Neointima was most prominent on the abluminal (outer) side of ePTFE membrane (between the ePTFE membrane and the internal elastic membrane) for the Jostent (Fig 2a) and predominantly abluminal (between the fluorinated ethylene propylene and PTFE membranes and the internal elastic membrane) for the Hemobahn (Fig 2b), but accumulations of luminal neointima formation were also present. In these cases, the neointima consisted of partly organized SMCs within a collagen matrix. Also in these grafts, the luminal neointima was focal and consisted of poorly organized SMCs within a collagen matrix, with interspersed bare areas of the graft exposed to the lumen. Review of the histologic sections from the Wallgraft (Fig 2c) demonstrated predominantly luminal neointimal formation consisting of spindle-shaped SMCs. The SMCs covered the lumen in its entirety with abundant extracellular matrix. At the lumen surface, the SMCs were more circumferentially organized and had a higher cellular density compared with cells adjacent to the stent wires (Fig 2c). Neointima formation with use of the Wallstent (Fig 2d) was minimal, with neointima consisting of SMCs in a proteoglycan-collagenous matrix which covered the stent struts. The internal elastic lamina was intact in all sections, indicating an absence of deep vessel wall injury.

Mild media compression was noted for all stents, especially at the areas of the stent struts. In other locations, the media was of normal thickness and appearance. Scattered inflammatory cells were sparse, adjacent to the stent wires in the Wallstent (inflammation

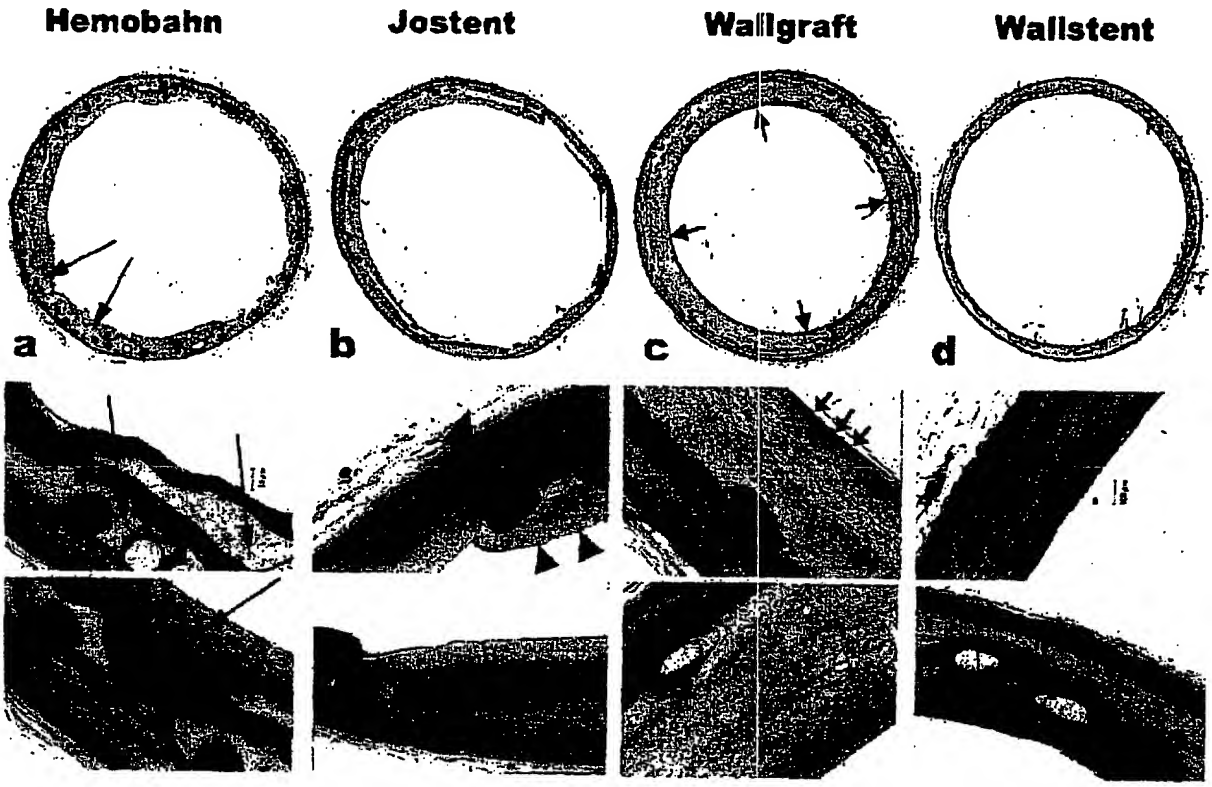

Figure 2. Representative hematoxylin and eosin-stained sections on low-power (upper rows) and high-power (middle and lower rows) photomicrographs (magnification ×100, scale bars are indicated) of iliac arteries 3 months after placement of the Hemobahn (a), Jostent (b), Wallgraft (c), and Wallstent (d). (a) Note marked abluminal neointimal formation with abundant proteoglycan-rich matrix (upper and middle rows, long arrows) adjacent to the ePTFE cover for the Hemobahn, but little accumulation of luminal neointimal formation is present (long arrows, lower row). Macrophage infiltration is present but solitary and focal. Neoangiogenesis (asterisk) in the neointima is present (middle row). (b) The neointima after Jostent placement contains organized SMCs with minimal matrix at the luminal surface (arrowheads, middle row). Note compression of media at the stent wire site (single arrowhead in the middle and lower column). (c) The Wallgraft has massive luminal neointima formation with proteoglycan-rich matrix and denser SMC formation near the lumen (short arrows). Macrophage infiltration is present but solitary and focal. Neoangiogenesis (asterisk) in the neointima is present (lower row). (d) The Wallstent has only minimal neointimal formation and demonstrates mild compression of the media at the stent wire site (with the wires removed during grounding of the methacrylate-embedded section). All high-power photomicrographs (middle and lower rows) demonstrate absence of inflammatory vessel wall changes or thickening for all prostheses.

score: 0.16 ± 0.01) and around the stent struts and graft material in the stent-grafts. The degree of inflammatory reaction was minimal and comparable for the Jostent (0.58 ± 0.03) and Wallgraft (0.55 ± 0.04) and significantly greater for the Hemobahn (0.83 ± 0.03), but the absolute difference between the stent-grafts is negligible (0.25 and 0.28, respectively). Neovascularization within the neointima was most prominent for the Hemobahn (Fig 2a), found to a lesser extent for the Wallgraft (Fig 2c), and almost completely absent for the Jostent and Wallstent (Table 2)

Scanning Electron Microscopy

Scanning electron microscopy demonstrated incomplete endothelialization of for all prostheses, although the differences were not significant ($P = .22$; Wallstent, 61.9% ± 9.9%; 95% CI, 38.7%–85.1%; Hemobahn, 41.3% ± 9.6%; CI, 19.3%–63.3%; Jostent, 44.3% ± 6.7%; CI, 28.8%–59.7%; Wallgraft, 37.2% ± 6.5%; CI, 22.3%–52.0%). The endothelium for the Wallstent was more mature, composed of spindle-shaped cells, and for the Hemobahn, when present, the endothelium was polygonal-shaped and immature. The endothelium for the Jostent and Wallgraft were almost equally composed of spindle- and polygonal-shaped cells (Fig 3).

DISCUSSION

Previous comparative studies had used predominantly homemade devices or stent-grafts currently withdrawn from the market (13,15–18). Consequently, it was important for us to use currently available stent-grafts—the Hemobahn (8,19), the Wallgraft (9,10), and the Jostent (11,20)—and additionally compare them to a bare stent, the Wallstent,

Table 2
Histomorphometric Analysis of Patent Lumen Area, Neointimal Area (in mm² ± SEM), Neointimal Thickness, and Media Thickness (in mm ± SEM)

		n	Mean	SEM	95% CI for Mean		ANOVA P Value
					Lower Bound	Upper Bound	
Lumen area	Hemobahn	18	42.57	1.41	39.59	45.54	
	Jostent	18	39.76	2.04	35.46	44.05	
	Wallgraft	18	40.22	1.04	38.02	42.42	
	Wallstent	18	41.64	1.59	38.27	45.00	.566
Neointimal area	Hemobahn	18	9.88	0.94	7.89	11.86	
	Jostent	18	6.52	0.46	5.55	7.48	
	Wallgraft	18	14.98	0.90	13.08	16.88	
	Wallstent	18	5.24	0.62	3.92	6.55	<.001
Luminal neointimal area	Hemobahn	18	1.66	0.45	0.72	2.60	
	Jostent	18	1.23	0.39	0.42	2.05	
	Wallgraft	18	14.05	0.90	12.16	15.94	
	Wallstent	18	0.28	0.16	−0.06	0.61	<.001
Media area	Hemobahn	18	5.21	0.53	4.10	6.31	
	Jostent	18	3.80	0.25	3.27	4.32	
	Wallgraft	18	6.08	0.11	5.85	6.31	
	Wallstent	18	5.26	0.24	4.75	5.77	<.001
Inflammation score	Hemobahn	18	0.83	0.03	0.77	0.89	
	Jostent	18	0.58	0.03	0.51	0.65	
	Wallgraft	18	0.55	0.04	0.46	0.64	
	Wallstent	18	0.16	0.01	0.13	0.19	<.001

Note.—ANOVA *P* values are indicated for each group of measurements. Histopathologic evaluation of the inflammatory reaction of the vessel wall (inflammation score) is graded from 0 (absent) to 3 (severe).

which is one of the most widely used stents. In comparative experimental (15,18) and clinical studies (17), polyester-covered stent-grafts (namely the Cragg EndoPro stent-graft) have caused massive inflammation to the vessel wall as well as systemic symptoms such as fever and elevated c-reactive protein, which was later termed postimplantation syndrome (16). These changes were not observed in experimental studies with other polyester-covered stent-grafts or when ePTFE-covered stent-grafts were used in larger clinical studies (8,11,13).

The key determinant of a stent's performance—patent lumen area at follow-up—was not significantly different among the prostheses in our direct comparison. These results were obtained by quantitative angiography and confirmed by histomorphometry. Early lumen gain and late lumen loss were also not significantly different. There was no hemodynamically significant luminal obstruction in the prostheses or at the perianastomotic region. Still, there is considerably more induction of neointima by the stent-grafts than the bare stent, but at least this did not affect patent lumen area in the current study. The induction of neointima was different between the ePTFE- and polyester-covered stent-grafts. After Wallgraft placement, luminal neointima formation was typically observed, perhaps after thrombus formation on the luminal side of this polyethylene terephthalate–covered graft. Polyester seems to facilitate early luminal thrombus formation, resulting in enhanced neointima formation (13). In contrast, after Jostent and Hemobahn placement, neointima induction was most prominent between the graft material and the vessel wall. The neointima can be attributed to the vascular wall reaction generated by these ePTFE-covered stent-grafts. When we compare the resulting lumen loss to neointima, the ePTFE-covered stent-grafts performed significantly better than the Wallgraft, with less neointima, but significantly more neointima was formed than after Wallstent placement. The term "anastomotic neointimal hyperplasia," originally coined by Okhi et al (21), refers to significant neointima formation at the "proximal and distal anastomosis," the border zone between the stent-graft and the native artery. However, this was more often observed in experimental studies with homemade devices (16,21–23) than with commercially available stent-grafts, with only one exception (10). Neointima formation after bare stent placement is also significant at this transition zone, maybe as a result of marked difference between the compliance of the stent and the pulsating movements of the arterial wall, which leads to low shear, consequently enhancing neointima formation (24,25).

We have also demonstrated that the biocompatibility of polyester or ePTFE (Wallgraft and Jostent) did not differ significantly and that both lead to minimal inflammatory wall changes. In absolute numbers, the differences between these stent-grafts and the bare stent were significant but small. We conclude that vascular wall changes observed were minimal for all prostheses but still favor bare stents.

The more rigid, balloon-expandable Jomed peripheral stent-graft induced significantly more medial atrophy. Chronic pressure exerted by radial forces on the vascular wall leads to medial thinning (26). The self-expanding prostheses induced less media atrophy.

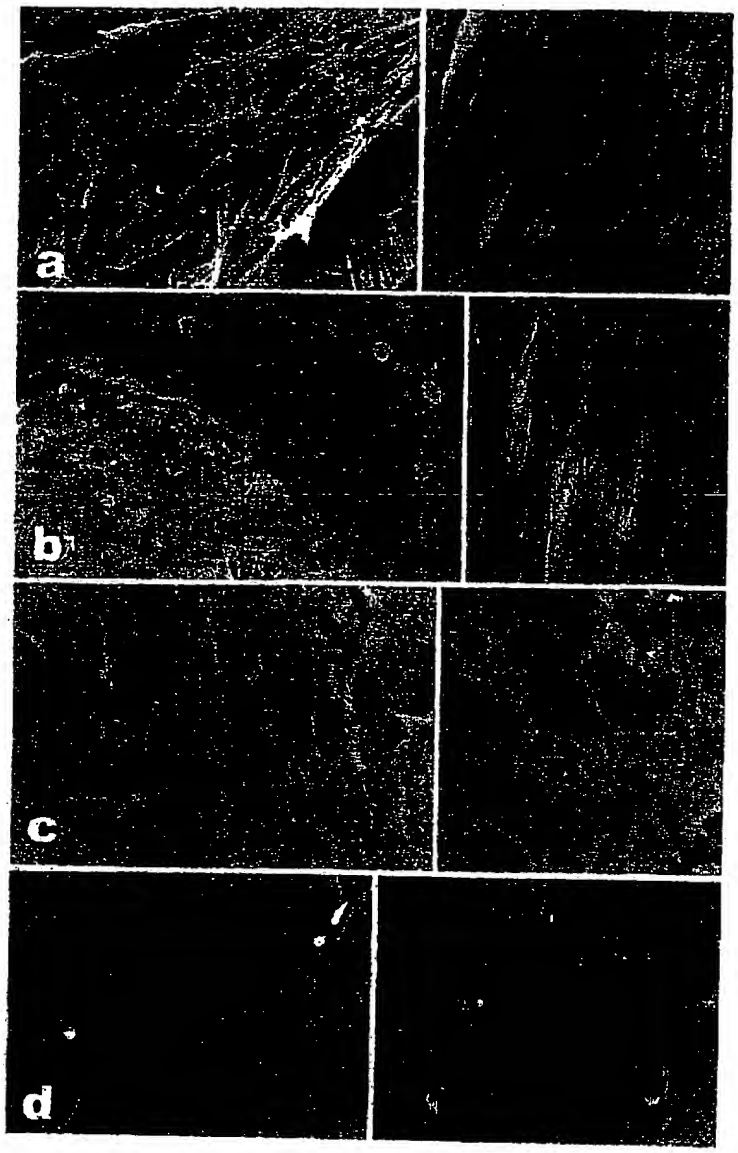

Figure 3. Scanning electron microscopy demonstrates incomplete endothelialization for all prostheses at 500× magnification. The Hemobahn stent-graft has predominantly immature endothelium (a). The Jostent (b) and Wallgraft (c) both have less than 50% uncovered areas, with mixed areas of predominantly immature polygonal cells, although the Wallgraft and Jostent also have spindle-shaped cells in some areas. The Wallstent has more than 60% endothelialization with predominantly mature, spindle-shaped endothelium (d).

Endothelialization was not significantly different among the prostheses used. Endothelialization was incomplete and the endothelium was immature. In previous studies, delayed endothelialization had been reported for ePTFE grafts, especially at the center portion of the grafts (13,19).

The main limitation of our study was that we implanted the protheses in healthy vessels. Although induction of atherosclerotic lesions would have been desirable from the standpoint of clinical correlation, composition and degree of the atherosclerotic plaque would have been variable and would have interfered with the primary aim of comparing biologic response with only the stent itself as the variable. The information provided by this study can help to achieve a more rational choice of stent-grafts for clinical application. Stent-grafts can be used for the treatment of complications of angioplasty or stent placement without fearing potential negative sequelae like enhanced neointima formation and/or inflammatory reaction. If stent-grafts are used for the treatment of complex stenoses by induction of anastomotic neointima formation, lumen narrowing might still be an issue in smaller-diameter vessels (10), but this was not the experimental setup of our study. With respect to clinical relevance, we conclude that the performance and biocompatibility are similar for all stent-grafts; however, the differences between bare stents and stent-grafts were detectable, but minimal.

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